IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Bernd RIEDL et al.		Confirmation No.:	1010
Serial No.:	09/993,647	Examiner:	Deepak R. RAO
Filed:	November 27, 2001	Group Art Unit:	1624

Title: ω-CARBOXYARYL SUBSTITUTED DIPHENYL UREAS AS RAF KINASE INHIBITORS

REPLY BRIEF

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer mailed December 23, 2004, herewith is Appellant's Reply Brief.

The Reply Brief is presented in response to the following new points of argument raised in the Examiner's Answer:

1) On page 6, line 3, of the Examiner's Answer, the breadth of the instant claims is misstated as embracing the treatment of "all diseases mediated by raf kinase." Method claim 74 is directed to the treatment of "cancerous cell growth mediated by raf kinase," and dependent claims 80, 81, 87 and 93 define more specific cancers. The Examiner clearly recognizes that the method claims are directed to the treatment of cancer and makes reference to this fact throughout the Examiner's Answer. This statement appears to be a mere oversight.

2) The Examiner's Answer cites the case *In re Buting*, 163 USPQ 689 (CCPA 1969) in maintaining the rejection under 35 USC §112, first paragraph. The breadth of the instant claims and the evidence are different here from those present in *Buting*. In addition, substantial progress has been made in the study and treatment of cancer in the intervening

years. These were found to be significant factors in reversing a rejection under 35 U.S.C. §§ 101 and 112 of claims that encompass the treatment of humans where the specification disclosed only *in vitro* studies and animal tests in *Ex parte Chwang*, 231 USPQ 751 (BOPA 1986).

3) The Examiner still has not presented any evidence or adequate reason for maintaining the rejection under 35 U.S.C. § 112, first paragraph of claims 74, 80, 81, 87 and 93. The Examiner is requiring that the application meet clinical standards as set by the FDA to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph in setting the following requirements:

> Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic end points are critical for electing the optimal dose and schedule. A detailed understanding of the molecular mode of action of RAF kinase inhibitors alongside the elucidation of the molecular pathology of individual cancers is required to identify tumor types and individual patients that may benefit most from treatment. It is also important to construct a pharmacological audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to tumor response end points. (Page 9, line 17–page 10, line 1)

The clinical trials referred to by the Examiner are for determining efficacy and safety, which is beyond what is necessary to satisfy the enablement requirement of 35 USC §112, first paragraph. As stated in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1442, (Fed. Cir. 1995) with respect to the utility requirement,

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs will prevent any companies from obtaining patent protection on the promising new invention, thereby eliminating an incentive to pursue, through research and development, potential cures in any crucial area such as the treatment of cancer.

This rationale translates to prescribing the disclosure necessary to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. As stated in *In re Anthony*, 414

F2d 1383, 162 USPQ 594, 604 (CCPA 1969), "Approval by the FDA, is not a prerequisite for the patenting of a new drug." As to the issue of safety, *In re Anthony* held,

> ...Congress has given the responsibility to the FDA, not the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use that they can be introduced in the commercial market, under the conditions prescribed, recommended or suggested in the proposed labeling thereof, as the majority of this court noted in *Hartop*, 135 USPQ at 426, 427.

4) Appellants maintain the teachings within the references cited in the instant specification are inconsistent with the Examiner's reasoning for maintaining the rejection. The Examiner's Answer states at page 8, lines 16-17, that, "The references are specific with respect to limited types of cancerous growth or malignancy." However, Monia et al., for example, states in their abstract,

> These studies strongly suggest that antisense inhibitors targeted against the C-raf-1 kinase may be of considerable value as antineoplastic agents that display activity against a wide spectrum of tumor types at well tolerated doses.

Monia et al. tested only a breast carcinoma cell line and a bladder carcinoma cell line, as well as A549 tumor in nude mice.

In addition, Fridman et al., another reference cited in the specification, states,

> Such a drug (a specific anti-Ras chemical drug) would be potentially useful for the treatment of Ras-associated cancers, which represent about 30% of total human carcinomas, notably more than 90% of pancreas carcinomas and 50% of colon carcinomas.

5) It is alleged that applicants have not identified any state of the art references that clearly establish correlation between the assays employed in the specification and clinical efficacy for the treatment of the claimed diseases. Such a showing is not necessary here. The specification provides an objectively enabling disclosure and there is no necessity for any data at all. In any event, the party in interest is a pharmaceutical manufacturer, which would only use assays which were reasonably correlated with efficacy to find new products.

6) Applicants maintain their reliance on *In re* Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) is appropriate in that they only relied on this citation for the general legal principle that an applicant is not required to test the claimed compounds in their final use. This case is not relied on for the underlying facts.

7) It is noted the Examiner's Answer has inconsistent statements with respect to the state of the art of cancer treatment. On page 13, line 1, the Examiner's Answer states "...Miller reference clearly teaches the use of diphenyl urea compounds in the treatment of various diseases (see starting in page 6) including cancer, lymphoid malignancies, etc.," (see page 7) which are the same diseases intended by the instantly claimed method, see claims 80, 81, 87 and 93." In contrast, on page 8, starting on line 14, the Examiner's Answer states "Further, the state of the art is not indicative of the fact that treatment of all types of cancerous cell growth or solid cancers mediated by raf kinase is conventional or well known."

8) In maintaining the rejection of method claims 74, 80, 81, 87 and 93 under 35 U.S.C. § 103 in view of Miller, it is alleged at page 13, line 8 of the Examiner's Answer that, "...the reference inherently teaches the instantly recited activity or mode of action of inhibition of raf kinase activity," and at page 13, line 11, "This biological property is inherently possessed by the reference compounds, particularly because the compounds are used in the same therapeutic application as recited in the instant claims." The Examiner's theory of inherency cannot support an obviousness rejection. Inherency and obviousness are distinct concepts." *Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 230 USPQ 81 at 83 (Fed. Cir. 1986) on rehearing 231 USPQ 160 (Fed. Cir. 1986). "Obviousness cannot be predicated on what is unknown." *In re Sporman and Heinke*, 363 F.2d 448, 150 USPQ 449, 451 at 452 (CCPA 1966). A retrospective view of inherency is not a substitute for some teaching or suggestion that the compounds of Miller are suitable for treatment of diseases mediated by raf kinase. See *In re Newell*, 841 F.2d 849, 13 USPQ2d 1248 at 1250 (Fed. Cir. 1984). Therefore, the Examiner's theory that the compounds of Miller inherently possess RAF kinase inhibiting activity does not support the rejection of the method claims herein directed to treating cancerous cell growth mediated by RAF kinase.

9) In the paragraph bridging pages 15 and 16, the examiner attempts to distinguish *Baird* from the current situation based on its facts. However, such a more

detailed comparison of the facts illustrates just how controlling *Baird* is in this appeal. The examiner alleges a difference from *Baird* in that he has pointed out specific compounds in the reference which are allegedly structurally analogous to the claimed compounds and which, therefore, allegedly provide motivation to change reference compound 34 in the way required to arrive at one of the claimed compounds. More specifically, the examiner simply states that because the reference compound 34 differs from the particular claimed compound at issue merely by the –CONHMe group, it would be obvious to insert the latter group into the proper site in reference compound 34 because of other generic disclosures in the reference establishing that this is a possibility.

But this is exactly the *Baird* situation. The structural difference in *Baird* was that the reference had two terminal -$OCH_2CH_2CH_2OH$ groups in bisphenol A polyester compounds, whereas *Baird*'s claimed compounds were identical except for two terminal OH groups. Thus, a single reference disclosed hydroxy as a possible substituent in the same location as the reference's hydroxypropoxy groups. Does the Examiner maintain that the –CONHMe group at issue here is a lesser structural distinction than is the differentiating –$OCH_2CH_2CH_2$- group at issue in *Baird*?

The court held in *Baird* that this structural difference taught away from *Baird*'s hydroxy groups. Similarly, here, the structure of reference compound 34 teaches away from the generic disclosure of the reference which includes the possibility that –CONHMe groups can be included. As in *Baird*, the reference does not provide the necessary motivation to support a rejection under 35 U.S.C. 103.

The examiner's discussion on pages 16 and 17 only makes sense with a very strong dose of improper hindsight. The examiner's rationale properly starts with reference compound 34 but then immediately proceeds to an improper analysis. The proper procedure is for the examiner to look at the totality of the cited reference and point to passages where it is suggested that a compound like reference compound 34 should have the -CONHMe group specifically substituted thereon, and specifically in the 3-position of the 4-methoxy-substituted phenyl ring. As explained in applicant's brief, there is absolutely no suggestion, i.e., no motivation, to make this change which is necessary to arrive at the claimed compound.

The examiner's improper procedure in essence poses the question: where can I look in this reference to find some sort of suggestion to place into the 3-position of the phenyl ring,

the methylcarbamoyl substituent? This is very different from the proper question which is simply to ask where in the reference is there any motivation to change reference compound 34 at all? The difference between these two questions is the mentioned very heavy dose of improper hindsight.

When the proper question is asked, the answer is that there are a very large number of possible changes to reference compound 34 which are mentioned in the reference and these include a wide variety of substituents and a wide variety of locations on the molecule. Even if any are particularly motivated, it is clear that the one necessary to arrive at the subject claimed compound is not. Thus, the examiner's comments on pages 16 and 17 alleging clear motivation for the alleged one change are incorrect. If anything, the reference only mentions the possibility of a very large number of changes, i.e., at best states that one "could" make many changes but in no way points to any particular change which arrives at the compound of interest.

10) As to the examiner's attempted distinction from the *Jones* case, this also is incorrect. In fact, *Jones* did also involve a single reference rejection where the genus "substituted ammonium salts," was generically taught as well as various examples. The PTO had alleged that each of these examples provided the motivation necessary to arrive at the particular cation at issue in *Jones* because these prior art examples contained structural features of the claimed cation. The court found that, even if the PTO were correct, merely because one allegedly could take certain views of the prior art compounds and could find certain suggestions, this was insufficient. There was nothing in the reference that motivated a skilled worker to do so for any reason.

11) As for the cases cited by the examiner on pages 17 and 18, these are all either irrelevant or much further removed from the issues on appeal than *Baird* and *Jones*.

This *Schaumann* case deals with when a "very limited number of compounds" can be anticipatory. This has nothing to do with any issue on appeal. In *Deuel*, the court found that a protein sequence was not sufficient to render obvious the corresponding particular DNA sequence. This is irrelevant to the facts at hand. In *Dillon*, the court found that discovery of a new use of an obvious composition does not render the composition non-obvious until actual unexpected properties are shown. Again, this has nothing to do with the issues on appeal. The claims in *In re Lamberti* were directed to a subgenus of compounds encompassed by the disclosure of two references. The inventive feature was said to comprise

using asymmetric dialkyl moieties. This is not a selection of an individual species from the broad genus defined by a Markush group, as is the case of the present invention. The claimed compounds at issue in *In re Payne* were defined by a generic heterocyclic structure having two sulphur atoms and a carbamyloximino moiety. These compounds were not encompassed by broad prior art disclosures.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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